ATTACHMENT A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	10/531,161	Confirmation No.	4723
Applicant	:	Shcherbakova et al.		
Title	:	QUINAZOLINONE COMPOUNDS AS CALCILYTICS		
Filed	:	April 12, 2005		
TC/A.U.	:	1624		
Examiner	:	Tamthom Ngo Truong		
Customer No.	:	32642		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AND RESPONSE TO OFFICE ACTION

Dear Sir:

In response to the Office Action of January 16, 2007, please amend the above-identified application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

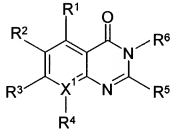
Remarks/Arguments begin on page 8 of this paper.

Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

Claim1 (currently amended) A compound having the chemical formula:



wherein:

R^1, R^2 and R^3 is each independently chosen from: H, halogen, CN, CF_3, OCF_3, lower alkyl, lower alkoxy, NH-acetyl, NH-lower alkyl, NH-alkylaryl, N(lower alkyl)$_2$, C(O)OH, C(O)O-lower alkyl, C(O)NH-lower alkyl, C(O)N(lower alkyl)$_2$, OH, OC(O)-lower alkyl, OC(O)-lower alkylamino, OC(O)-lower alkyl-N(lower alkyl)$_2$, and OP(O)(OH)$_2$;

R^4 is chosen from: H, halogen, CN, CF_3, OCF_3, lower alkyl, lower alkoxy, NH-acetyl, NH-lower alkyl, NH-alkylaryl, N(lower alkyl)$_2$, C(O)OH, C(O)O-lower alkyl, C(O)NH-lower alkyl, C(O)N(lower alkyl)$_2$, OH, OC(O)-lower alkyl, OC(O)-lower alkylamino, OC(O)-lower alkyl-N(lower alkyl)$_2$, and OP(O)(OH)$_2$;

X^1 is selected from one of C and N, such that when X^1 is N, then R^4 is absent;

R^5 is chosen from: H, a thienyl, styryl, pyridyl and phenyl group, wherein the thienyl, styryl, pyridyl and phenyl group is optionally substituted with 1 to 3 substituents chosen from: H, halogen, CN, CF_3, OCF_3, lower alkyl, NH-alkylaryl, N(lower alkyl)$_2$, OH, OC(O)-lower alkyl, OC(O)-lower alkylamino, OC(O)-lower alkyl-NH-lower alkyl, OC(O)-lower alkyl-N(lower alkyl)$_2$, and OP(O)(OH)$_2$;

R^6 comprises $-(CH_2)_n-X^2-R^7$ wherein n is 1, [[or]] 2 or 3, X^2 is O, C(O), CH(OH), ~~lower alkyl~~ or a single bond, and

R^7 is chosen from a pyridyl and a phenyl group, wherein R^7 is optionally substituted with 1 to 3 substituents chosen from: H, halogen, CN, OCF_3, unsubstituted lower alkyl, NH-alkylaryl, OC(O)-lower alkyl, OC(O)-lower alkylamino, OC(O)-lower alkyl-N(lower alkyl)$_2$, and OP(O)(OH)$_2$;

or a pharmaceutically acceptable salt or complex thereof;

wherein the compound has a Calcium Receptor Inhibitor Assay IC_{50} value of no greater than 30 μM ~~or lower~~.

Claim 2 (original) A compound according to claim 1, wherein R^1, R^2, R^3, and R^4 are independently selected from one of hydrogen, halogen, lower alkyl, OH and OP(O)(OH)$_2$.

Claim 3 (original) A compound according to claim 2, wherein said halogen is selected from one of fluorine and chlorine.

Claim 4 (original) A compound according to claim 2, wherein lower alkyl is methyl.

Claim 5 (original) A compound according to claim 2 wherein, R^1 is selected from one of hydrogen and methyl.

Claim 6 (original) A compound according to claim 2, wherein R^2 is selected from one of hydrogen, fluorine, chlorine, hydroxy, and methyl.

Claim 7 (original) A compound according to claim 2, wherein R^3 is selected from one of hydrogen and chlorine.

Claim 8 (original) A compound according to claim 2, wherein R^4 is selected from one of hydrogen, hydroxy, and methyl.

Claim 9 (original) A compound according to claim 1, wherein X^1 is carbon.

Claim 10 (original) A compound according to claim 1, wherein R^5 is phenyl optionally substituted with 1 or 2 hydroxy.

Claim 11 (original) A compound according to claim 1, wherein R^6 further comprises the group $-(CH_2)_n-X^2-R^7$;

wherein n is 1 or 2;

X^2 is a single bond, and

R^7 is phenyl optionally substituted with 1 or 2 halogens.

Claim 12 (original) A compound according to claim 11, wherein n is 2 and said halogens are selected from one of fluorine and chlorine.

Claim 13 (original) A pharmaceutical composition comprising a compound according to claim 1 and pharmaceutically acceptable diluent or excipient.

Claim 14 (previously presented) A method of treating a disease or disorder characterized by abnormal bone or mineral homeostasis chosen from: osteosarcoma, periodontal disease, fracture healing, osteoathritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia malignancy, and osteoporosis, comprising the administration to a subject in need of treatment thereof an effective amount of a compound according to claim 1.

Claim 15 (cancelled)

Claim 16 (original) A method according to claim 14, wherein the bone or mineral disease or disorder is osteoporosis.

Claim 17 (previously presented) A method of increasing serum parathyroid hormone levels in mammals for treatment of a disease or disorder chosen from: osteosarcoma, periodontal disease, fracture healing, osteoathritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia malignancy, and osteoporosis, which comprises the administration to a subject which may be benefited thereby an effective amount of a compound according to claim 1 sufficient to increase serum parathyroid hormone levels.

Claim 18 (original) A method for preparing 2,3,5,6,7,8-substituted 3*H*-quinazolin-4-ones by reacting 2,4,5,6,7,8-substituted benzo[*d*][1,3]oxazin-4-ones with primary amines under microwave irradiation conditions.

Claim 19 (previously presented) A compound selected from one of:
2-(2-hydroxy-phenyl)-3-phenethyl-3*H*-quinazolin-4-one;
2-(2,5-dihydroxy-phenyl)-3-phenethyl-3*H*-quinazolin-4-one;
2-(3-hydroxy-phenyl)-3-phenethyl-3*H*-quinazolin-4-one;
2-(2-hydroxy-phenyl)-3-(2-phenoxy-ethyl)-3*H*-quinazolin-4-one;
3-[2-(4-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-3*H*-quinazolin-4-one;
3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-3*H*-quinazolin-4-one;
3-[2-(2-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-3*H*-quinazolin-4-one;
3-[2-(3-chloro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-3*H*-quinazolin-4-one;
3-[2-(2-chloro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-3*H*-quinazolin-4-one;
2-(2-hydroxy-phenyl)-3-[2-(2-methoxy-phenyl)-ethyl]-3*H*-quinazolin-4-one;
2-(2-hydroxy-phenyl)-3-(2-*p*-tolyl-ethyl)-3*H*-quinazolin-4-one;
2-(2-hydroxy-phenyl)-6-methyl-3-phenethyl-3*H*-quinazolin-4-one;
6-fluoro-2-(2-hydroxy-phenyl)-3-phenethyl-3*H*-quinazolin-4-one;

6-chloro-2-(2-hydroxy-phenyl)-3-phenethyl-3*H*-quinazolin-4-one;

2-(2-hydroxy-phenyl)-3-phenethyl-5-phenethylamino-3*H*-quinazolin-4-one;

2-(2-hydroxy-phenyl)-5-methyl-3-phenethyl-3*H*-quinazolin-4-one;

7-chloro-2-(2-hydroxy-phenyl)-3-phenethyl-3*H*-quinazolin-4-one;

2-(2-hydroxy-phenyl)-8-methyl-3-phenethyl-3*H*-quinazolin-4-one;

6-fluoro-3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-3*H*-quinazolin-4-one;

6-fluoro-3-[2-(2-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-3*H*-quinazolin-4-one;

7-fluoro-3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-3*H*-quinazolin-4-one;

3-[2-(2-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5-methyl-3*H*-quinazolin-4-one;

3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-5-methyl-3*H*-quinazolin-4-one;

3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-6-methyl-3*H*-quinazolin-4-one;

3-[2-(2-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-6-methyl-3*H*-quinazolin-4-one;

6-chloro-3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-3*H*-quinazolin-4-one;

6-chloro-3-[2-(2-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-3*H*-quinazolin-4-one;

3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-6-methoxy-3*H*-quinazolin-4-one;

3-[2-(3-fluoro-phenyl)-ethyl]-6-hydroxy-2-(2-hydroxy-phenyl)-3*H*-quinazolin-4-one;

acetic acid 2-{6-fluoro-3-[2-(3-fluoro-phenyl)-ethyl]-4-oxo-3,4-dihydro-quinazolin-2-yl}-phenyl ester;

3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-8-methoxy-3*H*-quinazolin-4-one;

isobutyric acid 2-{6-fluoro-3-[2-(3-fluoro-phenyl)-ethyl]-4-oxo-3,4-dihydro-quinazolin-2-yl}-phenyl ester;

sodium salt of 6-fluoro-3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-3*H*-quinazolin-4-one;

8-chloro-2-(2-hydroxy-phenyl)-3-phenethyl-3*H*-quinazolin-4-one;

7-chloro-3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-3*H*-quinazolin-4-one;

7-chloro-3-[2-(2-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-3*H*-quinazolin-4-one;

2-(2-hydroxy-phenyl)-3-(2-pyridin-3-yl-ethyl)-3*H*-quinazolin-4-one;

6-fluoro-2-(2-hydroxy-phenyl)-3-(2-pyridin-3-yl-ethyl)-3*H*-quinazolin-4-one;

2-(2-hydroxy-phenyl)-3-phenethyl-3*H*-pyrido[2,3-*d*]pyrimidin-4-one;

3-[2-(3-fluoro-phenyl)-ethyl]-2-(2-hydroxy-phenyl)-3*H*-pyrido[2,3-*d*]pyrimidin-4-one;

3-(1,1-dimethyl-3-phenyl-propyl)-6-fluoro-2-(2-hydroxy-phenyl)-3*H*-quinazolin-4-one;

methylamino-acetic acid 2-{6-fluoro-3-[2-(3-fluoro-phenyl)-ethyl]-4-oxo-3,4-dihydro-quinazolin-2-yl}-phenyl ester hydrochloride;

6-fluoro-2-(2-hydroxy-phenyl)-3-(2-phenyl-propyl)-3*H*-quinazolin-4-one;

6-fluoro-2-(2-hydroxy-phenyl)-3-(*R*-2-phenyl-propyl)-3*H*-quinazolin-4-one;

6-fluoro-2-(2-hydroxy-phenyl)-3-(*S*-2-phenyl-propyl)-3*H*-quinazolin-4-one; ~~and~~

6-fluoro-2-(2-hydroxy-phenyl)-3-(3-phenyl-propyl)-3*H*-quinazolin-4-one

or a pharmaceutically acceptable salt or complex thereof.

REMARKS/ARGUMENTS

This Amendment is submitted in response to the Office Action mailed January 16, 2007. At that time claims 1-14 and 16-19 were pending in the application. In the Office Action, the Examiner withdrew the previous rejection under 35 U.S.C. §112, ¶¶ 1 and 2. The Examiner also found claim 19 to be allowable. However, the Examiner rejected claims 1-14 and 16-19 under 35 U.S.C. §112 ¶ 2 as being indefinite. Additionally, the Examiner rejected claims 1-3, 5-9 and 13 under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 4,710,502 issued to Wright, Jr. et al. (hereinafter "Wright, Jr.").

By this Amendment, claim 1 has been amended. Accordingly, claims 1-14 and 16-19 are presented for reconsideration by the Examiner.

REJECTION OF CLAIMS 1-14 and 16-19 UNDER 35 U.S.C. §112, ¶ 2

In the Office Action, the Examiner rejected claims 1-14 and 16-19 under 35 U.S.C. §112 ¶ 2 as being indefinite. *See* Office Action, page 2. The Applicants respectfully traverse this rejection.

The Examiner rejected claims 1-14 and 16-19 because of the element "the compound has a Calcium Receptor Inhibitor Assay IC_{50} value of 30 μM or lower." Applicants initially note that claim 19 does not depend from claim 1 and should not be included in the rejection under §112. By this Amendment, claim 1 was amended to recite "the compound has a Calcium Receptor Inhibitor Assay IC_{50} value of no greater than 30 μM." Exemplary support for this amendment can be found in the Present Application, page 66, lines 9-13. Therefore, no new matter has been added.

The Examiner has presented essentially three reasons why the element is allegedly indefinite. First, the Examiner argues that the original phrase "or lower" did not have definite metes and bounds because it technically includes an IC_{50} value of zero. *See* Office Action, page 2. Claim 1 was amended to recite an "IC_{50} value of no greater than 30 μM," thus avoiding the Examiner's concern that the claim covers IC_{50} values of zero.

Second, the Examiner argues, "[i]t is not clear what assay conditions are needed to obtain such an IC_{50} value. Thus, various factors could yield the same IC_{50} value for different set[s] of compounds." *See* Office Action, pages 2-3. As pointed out in the Amendment dated December 14, 2006, there is only one assay disclosed in the Present Application, and the conditions and procedure described is the assay are to be used to obtain the IC_{50} value recited in the claims. The assay used to determine the IC_{50} value for a claimed compound is clearly set forth on page 64, line 27 to page 66, line 13 and is titled "Calcium Receptor Inhibitor Assay." One having skill in the art would be able to routinely perform the assay using the procedure described to determine the IC_{50} value as claimed. Therefore, it is clear what assay conditions are needed to obtain the IC_{50} value recited in claim 1, and the element meets the requirements of 35 U.S.C. §112, second paragraph.

Third, the Examiner argues that the element provides functional language and does not "define any structural attributes." *See* Office Action, page 3. According to MPEP §2173.05(g), "There is nothing inherently wrong with defining some part of an invention in functional terms. Functional language does not, in and of itself, render a claim improper" (*citing In re Swinehart*, 439 F.2d 210 (CCPA 1971)). "A functional limitation is often used in association with an element, ingredient, or step of a process to define a particular capability or purpose that is served by the recited element, ingredient or step." MPEP §2173.05(g). In the present case, the recitation of "the compound has a Calcium Receptor Inhibitor Assay IC_{50} value of no greater than 30 μM" is used in association with the claimed structure to "define a particular capability...that is served by the recited [structure]."

Not only is this consonant with MPEP §2173.05(g), but it follows the direction provided in *In re Barr*, 444 F.2d 588, 595 (CCPA 1971), which states:

> The real issue in any such case [of determining definiteness] is not whether the recital is 'functional' or 'negative,' but whether the recital sets definite boundaries on the patent protection sought – that is, whether

those skilled in the relevant art can determine what the claim does or does not read on.

Judged by this standard, it is clear that the element of the claimed compound having an "IC_{50} value of no greater than 30 μM" complies with the second paragraph of §112 because, as described above, the specification provides a clear assay providing details necessary for one skilled in the art to determine whether or not the claim reads on a given compound. Therefore, the element meets the requirements of 35 U.S.C. §112, second paragraph. Withdrawal of this rejection is respectfully requested.

REJECTION OF CLAIMS 1-3, 5-9 and 13 UNDER 35 U.S.C. §102(b)

Claims 1-3, 5-9 and 13 were rejected under 35 U.S.C. §102(b) as being anticipated by Wright, Jr. *See* Office Action, page 3. Applicants respectfully traverse this rejection.

It is well settled that a claim is anticipated under 35 U.S.C. § 102(b) only if "each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP §2131, citing *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." MPEP §2131, citing *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

As a result of this paper, claim 1 was amended so that n is 1, 2 or 3 and X^2 does not include lower alkyl. Exemplary support for this amendment can be found on page 39 of the Present Application, compound 64, demonstrating a compound wherein n is 3. Therefore, no new matter has been added. Claims 1-3, 5-9 and 13 do not read on the compounds disclosed in Wright, Jr., namely, 6-chloro-3-[4-(3-pyridyl)butyl]-4(3H)-quinazolinone and 6-bromo-3-[4-(3-pyridyl)butyl]-4(3H)-quinazolinone (Table 1) because $n \neq 4$ and X^2 does not include lower alkyl. Because each and every claim element is not disclosed by Wright, Jr., the claims at issue are not anticipated. Withdrawal of this rejection is respectfully requested.

CONCLUSION

Applicants respectfully assert that claims 1-14 and 16-19 are patentably distinct from the cited reference, and request that a timely Notice of Allowance be issued in this case. If there are any remaining issues preventing allowance of the pending claims that may be clarified by telephone, the Examiner is requested to call the undersigned.

Respectfully submitted,

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